

## **REMARKS/ARGUMENTS**

As requested by the Examiner, Applicants affirm the provisional election made on 5/12/05 to prosecute the "invention of the rapamycin analogs, claim 22." Claim 22 has been amended accordingly. The above-noted Office Action is silent with regard any rejection pertaining to claim 22. Therefore, Applicants assume that claim 22 is allowable and respectfully requests that the Examiner pass this claim to issue.

Applicants also acknowledge that the Examiner has withdrawn claims 23 and 25 as being drawn to a non-elected invention. Despite the fact that the Examiner has withdrawn claim 25 from further consideration, the Examiner issued a 35 U.S.C. §112 rejection, second paragraph, regarding claim 25 and also rejected claim 25 under 35 U.S.C. §103(a). We believe the Examiner's statement regarding the withdrawal of claims 23 and 25 is an inadvertent error and that the Examiner meant to state that claims 23 and 24 have been withdrawn as being drawn to non-elected invention. This response is submitted accordingly.

Claims 1, 2, 5-7, 9, 11 and 21 and 25 are pending in the present application. Reconsideration of this Application and entry of this Amendment is respectfully requested.

### **Applicants' Present Invention**

To accommodate the Examiner and in the interest of prosecution efficiency, a brief non-limiting synopsis of the present invention follows.

Applicants' present invention is directed to peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist delivery. More specifically, the present invention includes PPAR $\gamma$  agonist eluding medical devices, wherein the devices include stents, catheters, microparticles, probes and vascular stents. The present application states, in part,

[0023] [t]he present invention includes novel compositions and methods for delivering peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists directly to tissues susceptible to restenosis. Specifically, the present invention is directed at implantable medical devices that provide for the *in situ*, site-specific controlled release of ligands that bind to and activate PPAR $\gamma$  receptors. Once activated, PPAR $\gamma$  receptors inhibit vascular smooth muscle cell (VSMC) proliferation.

[0031] In one embodiment of the present invention vascular stents are implanted into coronary arteries immediately following angioplasty.

However, one significant problem associated with stent implantation, specifically vascular stent deployment, is restenosis. Restenosis is a process whereby a previously opened lumen is re-occluded by VSMC proliferation. Therefore, it is an object of the present invention to provide stents that suppress or eliminate VSMC migration and proliferation and thereby reduce, and/or prevent restenosis.

[0032] In one embodiment of the present invention metallic vascular stents are coated with one or more anti-restenotic compound, specifically PPAR $\gamma$  agonists, more specifically the PPAR $\gamma$  agonists are thiazolidinediones.

Without reciting the entire text, Example 6-8 are included herein. This text may be found from paragraphs [0070] – [0088] in Applicants' present invention. Example 6 shows the inhibition of human coronary artery smooth muscle cells by ciglitazone, Example 7 shows the inhibition of human coronary artery endothelial cells by ciglitazone, and Example 8 shows the inhibition of human coronary artery smooth muscle cells by rosiglitazone.

### 35 U.S.C. §112 Rejections

Claim 25 has been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. More specifically, the Examiner states, "[i]n claim 25 'derivative' has no antecedent in claim 22. Is 'analogue' intended? Further '40-0' is indefinite. Is '40-O' intended? Claim 22 has been amended to include "derivatives of rapamycin" and claim 25 has been amended to include "40-O". Accordingly, claim 25 is believed to be definite. Therefore, Applicants respectfully request that the rejection be withdrawn.

### 35 U.S.C. §103 Rejections

Claims 1, 2, 5-7, 9, 11, 21, and 25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Hossainy *et al.* (USPN 6,153,252), in view of Dasseux (USPN 6,506,799) and Zenke *et al.* (USPN 6,239,124). More specifically, the Examiner states, "[i]t would have been obvious to one of ordinary skill to add rosiglitazone to the coated stent of Hassainy [*sic*] *et al* [*sic*] to achieve the beneficial effect of an additional agent to reduce the incidence of

restenosis in view of Dasseux and to replace rapamycin with the 40-O-(2-hydroxyethyl) derivative to achieve the beneficial effect of its improve pharmacokinetic properties in view of Zenke et al [*sic*].” Applicants respectfully disagree with this rejection.

In order to establish a prima facie case of obviousness, three basic criteria must be met, according to the Manual of Patent Examining Procedure, §706.02(j). These three are repeated as follows. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference(s) or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness regarding claims 1, 2, 5-7, 9, 11, 21, and 25.

In regard to the first criterion of obviousness, there is no suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine the reference teachings. Regarding the Hossainy *et al.* reference, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The Examiner states,

Hassainy [*sic*] et al [*sic*] teach coated stents (title). Reducing the incidence of restenosis is disclosed (column 1 [*sic*] lines 16-20). Polycaprolactone is specified (column 4 [*sic*] lines 22-24). Vascular stents are disclosed (column 14 [*sic*] lines 11-13). Delivery of therapeutic agents in the coating is specified (column 7 [*sic*] lines 56 et seq. [*sic*]). Rapamycin as an immunosuppressive is disclosed (column 8 [*sic*] line 32). Mixing one or more therapeutic agents in the coating is specified (column 8 [*sic*] lines 36-38).

Rather, more specifically, this reference teaches a process for coating stents. “The invention relates generally to a process for coating surgical devices. More specifically this invention relates to an improved process for coating stents and the like.” (Column 1, lines 7-10). Hossainy *et al.* does disclose a process for coating stents and various therapeutic and pharmaceutical agents that may be incorporated into the coating process. Also, the Examiner cites this reference because rapamycin is disclosed. However, Hossainy *et al.* does not disclose incorporating rosiglitazone into the coating.

It is important to note that rosiglitazone was known at least prior to November 13, 1997 (the filing date of USPN 5,859,037). Therefore, it is appropriate to conclude that Hossainy *et al.* had the opportunity to include rosiglitazone in its disclosure, and it did not do so. As a matter of fact, even though rosiglitazone was clearly known prior to the filing date of the Hossainy *et al.* reference, the Hossainy *et al.* reference is silent as to the entire class of thiazolidinediones, to which rosiglitazone belongs. Moreover, nowhere in the '252 patent is there any suggestion or motivation of the desirability to combine Hossainy *et al.* with the references discussed below.

Regarding the Dasseux reference, the Examiner states, "Dasseux teaches drug coated stents to reduce the risk of restenosis (abstract, column 117 [sic] lines 1-4). Rosiglitazone is specified (column 121 [sic] line 64)." Applicants respectfully disagree, in part, with the Examiner's characterization of this reference. The abstract discloses, "[t]he present invention relates to methods of treating cardiovascular disease, dyslipidemia, dyslipoproteinemia, and hypertension comprising administering a composition comprising an ether compound." Moreover, the reference only makes a mere passing mention of a stent. The actual word "stent" is used twice within the entire 152 column disclosure. Also, the compound rosiglitazone is mentioned only once in this voluminous reference. There is no mention in this reference of Applicants' present invention as described above. Rather, the reference discloses, in part, under the section heading "5.5. Surgical Uses of the Compounds of the Invention,"

[a]ccordingly, the *compounds of the present invention* may be used as coatings on surgical devices (e.g., catheters) and implants (e.g., stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.  
(Column 117, lines 1-6). (Emphasis added).

According to the disclosure of the Dasseux reference, "[t]he present invention provides *novel compounds* having the general formula I." (Emphasis added). (Column 21, lines 53-55). None of these compounds include a PPAR agonist, let alone a thiazolidinedione (the class to which PPAR agonists belong). Rather, the reference discloses,

[i]n certain embodiments of the invention, a compound of formula I or a pharmaceutically acceptable salt thereof is administered in combination with *another therapeutic agent*. The *other therapeutic agent* provides additive or

synergistic value relative to the administration of a compound of formula I alone. The therapeutic agent can be...a PPAR agonist.  
(Column 24, lines 34-40). (Emphasis added).

The Dasseux reference only refers to a PPAR agonist used in conjunction with a *compound(s) of the present invention*. The reference is void of any enabling disclosure of a rosiglitazone coated stent or the beneficial aspects of rosiglitazone, namely the anti-proliferative affects and benefits taught and enabled in Applicants' present invention. Rather, the Dasseux reference actually teaches away from "implantable medical devices that provide for the *in situ*, site-specific controlled release of ligands that bind to and activate PPAR $\gamma$  receptors...once activated, PPAR $\gamma$  receptors inhibit vascular smooth muscle cell (VSMC) proliferation" as required in Applicants' present invention. Dasseux does this by stating that "the compound of formula I or a pharmaceutically acceptable salt thereof is administered in combination with another therapeutic agent. The therapeutic agent can be...a PPAR agonist." Therefore, the Dasseux reference discloses that the only way a PPAR agonist may be used in accordance with their alleged invention is to use it with a "novel compound" of the Dasseux disclosure. Moreover, no where in this reference is there any suggestion or motivation of the desirability to combine Dasseux with the other references discussed herein.

Regarding the Zenke *et al.* reference, the Examiner states, "Zenke et al [*sic*] teach that the 40-O-(2-hydroxyethyl) derivative of rapamycin has improved pharmacokinetic properties (column 1 [*sic*] lines 50-53)." Notably, the Zenke *et al.* reference discloses a pharmaceutical composition for the treatment of transplant rejection or autoimmune or inflammatory conditions comprising cyclosporine A and 40-O-(2-hydroxyethyl)-rapamycin." (Title). This reference has been cited in response to a dependent claim, namely claim 22. Claim 22 depends from claim 21, and because claim 21 defines unobvious patentable subject matter, claim 22 also defines unobvious patentable subject matter.

In regard to the second criterion of obviousness, there is no reasonable expectation that the combination would be successful. Undoubtedly, even if one were to combine the references discussed herein, one would have to conduct undue experimentation to achieve Applicants' present invention. Whereas Applicants' present invention teaches one skilled in the art, among other things, how to coat a medical device using a drug/polymer system having a PPAR agonist, how to coat a medical device using a sandwich-type coating having a PPAR

agonist, and how to coat a stent with a PPAR agonist drug, none of the above-noted references, when considered alone or in combination, teach and enable any of the above. Moreover, Applicants' present application fully enables the present invention by providing the above-noted information in addition to the detailed and thorough data provided in Examples 6-8. Examples 6-8 show, among other things, significant proliferation inhibition of human coronary artery smooth muscle cells by ciglitazone (Example 6), significant proliferation inhibition of human coronary artery endothelial cells by ciglitazone (Example 7), significant proliferation inhibition of human coronary artery smooth muscle cells by rosiglitazone (Example 8). None of the above-noted references disclose, let alone enable one skilled in the art to practice the present invention. Therefore, because when taken alone or in combination, the above-noted references do not teach or enable one skilled in the art to practice Applicants' present invention, there can be no reasonable expectation that if one were to combine the references that this combination would be successful.

In regard to the third criterion of obviousness, the prior art references do not teach or suggest all the claim limitations. The above-noted references, taken either alone or together, do not teach or suggest at least a medical device having a site-specific delivery device for the controlled release of at least one peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonist (claim 1). Moreover, the above-noted references, taken either alone or together, do not teach or suggest a medical device including a stent having a coating comprising rosiglitazone and a polymer selected from the claim group (claim 11) or at least one additional therapeutic agent selected from the claimed group (claim 21). Accordingly, claims 1, 11 and 21 are in condition for allowance.

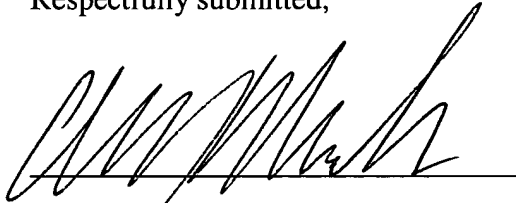
Claims 2, 5-7, 9, and 25 ultimately depend from claims 1, 11 and 21 and since these claims define unobvious patentable subject matter, claims 2, 5-7, 9, and 25 define unobvious patentable subject matter. Regarding the Zenke *et al.* reference, the reference was cited by the Examiner in view of claim 22. Claim 22 is a dependent claim that depends from claim 21 and, as noted above, because claim 21 defines unobvious patentable subject matter, claim 22 defines unobvious patentable subject matter.

All claims 1, 2, 5-7, 9, 11, 21, and 25 are believed to be in condition for allowance, and a Notice of Allowability is therefore earnestly solicited.

Conclusion

For the foregoing reasons, Applicants respectfully assert that all the pending claims are in condition for allowance and should be passed to issue. The Commissioner is hereby authorized to charge any additional fees which may be required under 37 C.F.R. 1.17, or credit any overpayment, to Deposit Account No. 01-2525. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at telephone (707) 543-0221.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Alan M. Krubiner', is written over a horizontal line.

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